The Brazilian Journal of
INFECTIOUS DISEASES

www.elsevier.com/locate/bjid

Original article

Relationship between viral load and behavioral measures of adherence to antiretroviral therapy in children living with human immunodeficiency virus in Latin America

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ARTICLE INFO

Article history:
Received 8 August 2014
Accepted 27 January 2015
Available online 3 March 2015

Keywords:
Pediatric
ART
Adherence
Latin America

ABSTRACT

Few studies have examined antiretroviral therapy adherence in Latin American children. Standardized behavioral measures were applied to a large cohort of human immunodeficiency virus-infected children in Brazil, Mexico, and Peru to assess adherence to prescribed antiretroviral therapy doses during the three days prior to study visits, assess timing of last missed dose, and evaluate the ability of the adherence measures to predict viral suppression. Time trends in adherence were modeled using a generalized estimating equations approach to account for possible correlations in outcomes measured repeatedly in the same participants. Associations of adherence with human immunodeficiency virus viral load were examined using linear regression. Mean enrollment age of the 380 participants was 5 years; 57.6% had undetectable' viral load (<400 copies/mL). At enrollment, 90.8% of participants were perfectly (100%) adherent, compared to 87.6% at the 6-month and 92.0% at the 12-month visit; the proportion with perfect adherence did not differ over time ($p = 0.1$). Perfect adherence was associated with a higher probability of undetectable viral load at the

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[1] Members of the NISDI PLACES (Pediatric Latin American Countries Epidemiologic Study) Study Group are shown in the Acknowledgements.

http://dx.doi.org/10.1016/j.bjid.2015.01.004

12-month visit (odds ratio = 4.1, 95% confidence interval: 1.8–9.1; $p < 0.001$), but not at enrollment or the 6-month visit ($p > 0.3$). Last time missed any antiretroviral therapy dose was reported as "never" for 52.0% at enrollment, increasing to 60.7% and 65.9% at the 6- and 12-month visits, respectively ($p < 0.001$ for test of trend). The proportion with undetectable viral load was higher among those who never missed a dose at enrollment and the 12-month visit ($p \leq 0.005$), but not at the 6-month visit ($p = 0.2$). While antiretroviral therapy adherence measures utilized in this study showed some association with viral load for these Latin American children, they may not be adequate for reliably identifying non-adherence and consequently children at risk for viral resistance. Other strategies are needed to improve the evaluation of adherence in this population.

Introduction

In 2012, there were approximately 56,000 children under 15 years of age living with HIV in Latin America and the Caribbean.[1] With increased availability of antiretroviral therapy (ART), there has been a significant decrease in the morbidity and mortality of perinatally infected children.[2,3] Success in achieving good outcomes relies on high levels of ART adherence to maximize clinical effectiveness and limit potential for development of drug resistance.[4]

Few studies from Latin America have estimated ART adherence levels in children or evaluated the validity of methods used to measure adherence.[5] Among the various methods used in resource-limited settings, behavioral measures of adherence, including self- and caregiver-report, are the most common.[6] Behavioral methods are attractive because they are practical and inexpensive. However, few studies in resource-limited settings have attempted to validate their accuracy by comparing them with other adherence measurement tools, and those that have produced mixed results.[7–12] In this substudy of the NICHD (*Eunice Kennedy Shriver* National Institute of Child Health and Human Development) International Site Development Initiative (NISDI) PLACES (Pediatric Latin American Countries Epidemiologic Study) protocol, we assessed ART adherence levels and evaluated the ability of the adherence measures to predict viral suppression among children living with HIV in Latin America.

Materials and methods

Participants

Participants were children living with HIV and their caregivers that enrolled in PLACES, a prospective cohort study that enrolled perinatally HIV-infected children less than 6 years of age at the time of enrollment at 14 clinical sites (12 in Brazil, 1 each in Peru and Mexico). The protocol was approved by the ethical review boards of each clinical site, the sponsoring institution (NICHD), the data management and statistical center (Westat), and the Brazilian National Ethics Committee (CONEP). Informed consent was obtained from the parents or guardians prior to enrollment.

A description of the earlier version of the protocol and the cohort, including the site selection process, has been published elsewhere.[13] In brief, demographic, laboratory, and clinical data were collected at enrollment and every 6 months, including HIV-1 RNA viral load (VL), CD4 measures, CDC classification, and antiretroviral medication adherence.

Adherence measures

ART adherence was assessed through a structured questionnaire developed for use by the U.S. National Institute of Allergy and Infectious Diseases (NIAID) as part of standard practice in PACTG (Pediatric AIDS Clinical Trials Group) studies.[14] The potential for social desirability bias with self-/caregiver-reported adherence was considered in the design of the PACTG instrument and the instructions for its administration, which were followed in our study. These instructions emphasize that the accuracy of self-report is very good if the attitude of the interviewer is non-judgmental and supportive. To set the proper tone, the adherence form includes introductory statements acknowledging how difficult adherence can be that were read verbatim. The participant/caregiver was asked to identify the ARV medications and number of doses (not number of pills) prescribed each day. The participant/caregiver was prompted regarding any omitted medications if all of the prescribed ARV medications identified during medical chart review by the interviewer were not reported. Interviewees were then asked to report the number of missed doses for each ARV medication for each of the previous three days. The interviewer asked about specific problems that may have been encountered in giving or taking medications. Instructions printed on the form stressed that any interaction occurring after the form was completed in response to non-adherence was critically important, noting that the attitude of the interviewer in response to non-adherence, the manner in which adherence would be promoted, and the nature of any behavioral counseling offered would absolutely influence the validity of subsequent self-report data.

The interview was administered in Spanish or Portuguese by a member of the clinical care or research team to the person with primary responsibility for medication administration. Certified translations were performed by an independent company using language experts (English and the relevant